Elevated cardiac troponin T contributes to prediction of worse in-hospital outcomes after endovascular therapy for acute limb ischemia

Birgit Linnemann, MD,[a,b] Thilo Sutter,[a] Sebastian Sixt, MD,[a] Aljoscha Rastan, MD,[a] Uwe Schwarzwaelder, MD,[a] Elias Noory, MD,[a] Karlheinz Buergelin, MD,[a] Ulrich Beschorner, MD,[a] and **Thomas Zeller, MD,[a]** *Bad Krozingen and Frankfurt/Main, Germany*

Introduction: **The present study evaluated whether elevated cardiac troponin T (cTnT) was predictive of an increased risk for death or amputation in patients with acute lower limb ischemia (ALI). ALI is one of the most frequent causes of amputation, with mortality rates for ALI ranging from 15% to 20%.**

Methods: **This study included 254 consecutive ALI patients (155 men, 99 women; mean age, 71.6 ± 13.2 years) presenting with Rutherford categories I, IIA, or IIB according to the classification for ALI.**

Results: **ALI was caused by thromboembolism (29.5%), local arterial thrombosis (53.1%), or bypass graft occlusion (16.9%). Restoration of arterial blood flow was obtained by an endovascular approach, with a primary success rate of 98.4%. Rates were low for in-hospital mortality (3.9%) and amputation (5.1%). Patients who died or required amputation more frequently presented with elevated cTnT ≥0.01 ng/mL (52.2% vs 25.5%, *P* = .01) and impaired renal function (chronic kidney disease stage 3-5; 60.9% vs 38.1%; *P* = .04). After controlling for age, sex, C-reactive protein, renal function, presence or absence of coronary artery disease, and traditional vascular risk factors, as well as the interval between symptom onset and revascularization, the relationship between cTnT and a worse in-hospital outcome remained significant (hazard ratio, 3.4; 95% confidence interval, 1.3-8.5; *P* = .010).**

Conclusions: **ALI patients frequently have elevated cTnT, which is associated with increased in-hospital mortality and amputation. Even small cTnT elevations predict a markedly increased risk of worse in-hospital outcome; however, the overall mortality and amputation rate in our study was low. (J Vasc Surg 2012;55:721-9.)**

The cardiac troponins are established markers of myocardial injury and necrosis. In the clinical setting of myocardial ischemia, evidence of increased cardiac troponins has been defined as the cornerstone of the redefinition of myocardial infarction.[1] Cardiac troponins are also elevated in patients with varying degrees of chronic kidney disease (CKD).[2] Among patients with end-stage renal disease (ESRD), elevated cardiac troponin T (cTnT) was found in 17% to 43% of patients, whereas elevated cardiac troponin I (cTnI) was found in 12% to 18% of patients.[3,4] However, there is evidence that this finding cannot be exclusively related to an accumulation due to renal failure. The increase in cardiac troponins is not correlated with creatinine concentration,[5] and elimination of cTnI was independent of renal function.[6] Furthermore, cTnT levels remain elevated even after successful renal transplantation.[7] In their meta-analysis of 28 studies, including 3931 patients with ESRD, Khan et al[8] suggested that increased levels of cTnT and cTnI are independent predictors of death.

Recently, some investigations have reported that elevated cardiac troponins may also be of prognostic value in patients with peripheral arterial occlusive disease (PAOD) with acute or chronic critical limb ischemia.[9-11] However, many PAOD patients have impaired renal function, and cardiac troponins often increase with declining glomerular filtration rate (GFR). Moreover, CKD itself is associated with increased cardiovascular death.[12,13] This study was performed to test the hypothesis that TnT is an independent risk indicator of a worse in-hospital outcome (ie, death or amputation), in PAOD patients with acute lower limb ischemia (ALI) of Rutherford categories I, IIA, and IIB.

METHODS

Study design. In a retrospective study design, we analyzed data of 260 consecutive ALI patients (161 men, 99 women) treated between January 2007 and December 2009. The protocol was approved by the local ethics committee and registered at http://ClinicalTrials.Gov (NCT01087385). The study cohort had an average age of 71.5 years (range, 20-98 years). ALI was defined as sudden onset or acute deterioration of clinical symptoms of lower limb ischemia (ie, severe claudication or rest pain) within the last 14 days. All patients included in this study were in the Rutherford clinical categories I, IIA, or IIB for ALI[14]

From the Department of Angiology, Heart Center Bad Krozingen, Bad Krozingen[a]; and Division of Vascular Medicine, Department of Internal Medicine, Johann Wolfgang Goethe University Hospital, Frankfurt/Main.[b]

Competition of interest: none.

Reprint requests: Birgit Linnemann, MD, Johann Wolfgang Goethe University Hospital, Frankfurt/Main Division of Vascular Medicine, Department of Internal Medicine, Theodor-Stern-Kai 7, D-60590 Frankfurt/Main, Germany (e-mail: birgit.linnemann@kgu.de).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2011.10.024

and underwent a primary endovascular approach to restore arterial blood flow.

Laboratory assessment. Blood samples were drawn at hospital admission. Cardiac TnT was measured using the fourth-generation assay Elecsys Troponin T on Cobas 6000 e601 systems (Roche Diagnostics, Mannheim, Germany), according to the manufacturer's recommendations. The 99th percentile value for the reference population used by the manufacturer of the assay was 0.01 ng/mL, and the lowest level at which the coefficient of variation was <10% was 0.03 ng/mL.[15] Two different cutoff criteria were used to define elevated cTnT: 0.01 ng/mL, which corresponds to the 99th percentile of a reference population and the lowest level of detection, and 0.03 ng/mL, which represents the cutoff value for the definition of myocardial necrosis with this assay using the 10% total imprecision coefficient of variation criteria.[16]

Laboratory testing also included automated and standardized testing of complete blood cell counts and serum levels of creatinine, C-reactive protein (CRP), fibrinogen, creatine kinase (CK), CK-MB, lactate dehydrogenase, and myoglobin. Blood sampling was repeated at least twice daily to assess maximum values of CK (CK_{max}) and myoglobin ($myoglobin_{max}$) during the hospital stay. The estimated GFR (eGFR) was determined by the Cockgroft-Gault formula and classified using the standards of the National Disease Outcomes Quality Initiative.[17] We defined CKD as an eGFR <60 mL/min.

Clinical evaluation and electrocardiograph registration. Six patients sustained an acute coronary syndrome (ACS) ≤14 days before the onset of ALI and were censored from further statistical analysis. There was no clinical evidence of myocardial ischemia among the remaining 254 patients. We analyzed patients' electrocardiograms (ECGs), which were performed simultaneously with blood sampling at the time of admission to the hospital. According to the consensus document of the Joint European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Redefinition of Myocardial Infarction,[1] we registered ECG changes that may be indicative of acute myocardial ischemia:

1. ST elevation at the J-point in two contiguous leads with the cutoff points of ≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads;
2. horizontal or down-sloping ST depression of ≥0.05 mV or T inversion of ≥0.1 mV in two contiguous leads, or both; and
3. the presence of left bundle branch block.

Patient outcomes. Differences in in-hospital outcome were determined for patients with elevated and normal cTnT concentrations. The primary end point was the rate of in-hospital death or amputation. Causes of death were determined from death certificates or medical reports.

Statistical analysis. Statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, Ill). In addition to obtaining descriptive statistics with the mean ± standard deviation (SD) or median and range, we performed the χ^2 test in cross-tabulations and the Mann-Whitney *U* test for comparison of metric variables. Differences in in-hospital outcome were compared between patients with elevated and normal cTnT concentrations. Unadjusted and adjusted hazard ratios (HRs) of the combined end point of death or amputation, and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. All adjusted models were fit with age, sex, coronary artery disease (CAD), established vascular risk factors, eGFR, and other variables differing in univariate analyses between the two groups. All tests were two-sided, and the criterion for statistical significance was $P \leq .05$.

RESULTS

Study cohort. Clinical characteristics and demographic information available for the study cohort of 254 ALI patients (61% men) are summarized in Table I. Mean patient age was 71.6 ± 13.2 years. Patients presented with clinical symptoms according to Rutherford categories I (36%), IIA (30%), and IIB (34%) for ALI. The localization or proximal extension of the arterial occlusion most often involved the femoral arteries (62.6%), followed by the popliteal artery (22.4%), iliac arteries (11.0%), and tibial or peroneal arteries (3.9%). Arterial occlusion was caused by arterial thromboembolism in 29.5% and by a local thrombotic process in 53.1%. Most of these involved normal-sized vessels with pre-existing atherosclerotic lesions, and an arterial aneurysm was detected as the cause of arterial occlusion in nine cases (6.7%). Bypass graft occlusions contributed to 16.9% of ALI cases. In only one patient could the cause of the arterial occlusion not be determined. Catheter-guided revascularization techniques included mechanical thrombectomy (61.8%), catheter thrombus aspiration (31.9%), local thrombolysis (53.1%), angioplasty and stent placement (76.0%), and atherectomy (2.0%).

Patient in-hospital outcomes. All patients underwent interventional recanalization procedures to restore arterial blood flow to the lower extremity, with an overall primary success rate of 98.4%. The mean time between the onset of symptoms and revascularization was 2.8 ± 2.6 days. The revascularization procedure was performed ≤24 hours after the onset of symptoms in 119 patients (46.5%) and ≤72 hours in 195 (76.8%). In four patients (1.6%), endovascular revascularization was not successful. Of these, two patients underwent emergency femoropopliteal bypass surgery on the same day, one patient underwent major amputation within the next few days, and one patient died in the course of the hospital stay.

The median duration of the hospital stay was 7.1 days (range, 1-57 days). Overall rates were 10 of 254 (3.9%) for in-hospital mortality and 13 of 254 (5.1%) for amputation, which were low. Major amputation was unavoidable in seven patients (2.7%), and six patients (2.4%) underwent minor amputation. Death was caused by progressive gangrene, septicemia, or systemic inflammatory response syndrome (SIRS), followed by multiorgan failure in eight

Table I. Clinical characteristics and demographics of the 254 study patients at baseline

Characteristics[a]	*Total cohort (n = 254)*	*In-hospital death or amputation (n = 23)*	*Amputation-free survival (n = 231)*	P[b]
Age, years	72 ± 13	77 ± 11	71 ± 13	.042
Male sex	155 (61)	13 (57)	142 (62)	.659
Vascular risk factors and comorbidities				
Current smoker	64 (25)	3 (13)	61 (26)	.211
Diabetes mellitus	75 (30)	7 (30)	68 (30)	>.99
Arterial hypertension	213 (84)	16 (70)	197 (85)	.070
Hypercholesterolemia	175 (69)	9 (39)	166 (72)	.003
Coronary artery disease	91 (36)	7 (30)	84 (36)	.654
Atrial fibrillation	78 (31)	8 (36)	70 (30)	.630
Prior cerebral infarction	25 (10)	2 (9)	23 (10)	.846
Prior peripheral revascularization				
Endovascular	118 (47)	8 (35)	110 (48)	.278
Bypass surgery	57 (22)	5 (22)	52 (23)	.932
Prior amputation	20 (8)	1 (4)	19 (8)	.556
Chronic kidney disease stages 3-5	102 (40)	14 (61)	88 (38)	.044
End-stage renal disease	9 (4)	2 (9)	7 (3)	.191
PAOD characteristics				
Rutherford category				
I	90 (36)	1 (4)	89 (39)	<.001
IIA	77 (30)	1 (4)	76 (33)	.003
IIB	87 (34)	21 (91)	66 (29)	<.001
Ankle-brachial index	0.19 ± 0.32	0.08 ± 0.03	0.20 ± 0.33	.020
Causes of acute limb ischemia				
Thromboembolism	75 (30)	8 (35)	67 (29)	.358
Local thrombosis	135 (53)	10 (44)	125 (54)	.384
Bypass graft occlusion	43 (17)	4 (17)	39 (17)	.870
Unknown	1 (0.4)	0	1	>.99
Proximal extension of arterial occlusion				
Iliac arteries	19 (7)	2 (9)	17 (7)	.685
Femoral arteries	161 (63)	15 (65)	146 (63)	.849
Popliteal artery	63 (2)	5 (22)	58 (25)	.721
Tibial or peroneal arteries	11 (4)	1 (4)	10 (4)	.997
Endovascular revascularization				
Mechanical thrombectomy	155 (61)	13 (57)	142 (62)	.642
Local thrombolysis	135 (53)	13 (57)	122 (53)	.828
Catheter thrombus aspiration	81 (32)	17 (74)	156 (68)	.643
Angioplasty/stenting	193 (76)	19 (83)	174 (75)	.610
Mechanical atherectomy	5 (2)	0 (0)	5 (2)	.476
Comedication on admission				
Antiplatelet therapy	230 (91)	12 (52)	210 (91)	<.001
Vitamin K antagonist	61 (24)	2 (9)	59 (26)	.078
Lipid-lowering drug	173 (68)	16 (69)	157 (68)	.875
β-blocker	156 (61)	17 (74)	139 (60)	.262
ACE inhibitor/AT1RA	188 (74)	20 (87)	168 (73)	.217

ACE, Angiotensin converting enzyme; *AT1RA,* angiotensin type 1 receptor antagonist; *PAOD,* peripheral arterial occlusive disease.
[a]Categoric data are presented as number (%) and continuous data as mean ± standard deviation.
[b]*P* values related to the comparison of in-hospital death or amputation vs amputation-free survival.

patients, hemorrhagic shock due to gastrointestinal bleeding after local thrombolysis in one patient, and aortic valve endocarditis with thromboembolic complications in another patient. No patients sustained a fatal myocardial infarction. Clinical characteristics available for the 23 patients who died or underwent amputation during the hospital stay and the 231 patients with amputation-free survival are summarized in Table I.

Elevated cTnT and in-hospital outcome. Patients with worse in-hospital outcome (ie, death or amputation) differed from those with amputation-free survival with regard to cTnT, CK, CK-MB, CK_{max}, lactate dehydrogenase, and $myoglobin_{max}$ (Table II). Levels for cTnT of ≥0.01 and ≥0.03 ng/mL were found in 52.2% and 34.8% of patients with worse in-hospital outcomes ($P = .01$), respectively, whereas 25.5% and 12.6% of patients with amputation-free survival had cTnT elevation ($P = .009$, respectively).

An elevated cTnT of ≥0.01 ng/mL was present in 71 ALI patients (28.0%) at admission to the hospital; and in 37 (14.6%), the cTnT levels were even ≥0.03 ng/mL. The cumulative rates for in-hospital death or amputation were 16.9% for patients with elevated cTnT (≥0.01 ng/mL) vs 6.0% for those with normal cTnT ($P = .01$). Corresponding results were found for patients with cTnT levels of ≥0.03 ng/mL (21.5%) vs <0.03 ng/mL (6.9%, $P = .009$). Unadjusted HRs were 2.8 (95% CI, 1.2-6.8) for cTnT

Table II. Laboratory parameters in patients with acute lower limb ischemia according to in-hospital outcome (death or amputation vs amputation-free survival)

Variable[a]	*In-hospital death or amputation (n = 23)*	*Amputation-free survival (n = 231)*	P
Cardiac troponin T			
≥0.01 ng/mL	12 (52.2)	59 (25.5)	.013
≥0.03 ng/mL	8 (34.8)	29 (12.6)	.009
Skeletal muscle enzymes			
CK, U/mL	973 ± 1143	284 ± 694	<.001
CK-MB, U/mL	36.6 ± 23.4	24.0 ± 35.4	<.001
LDH, U/mL	308 ± 116	204 ± 72	<.001
CK_{max}, U/mL	3893 ± 4846	769 ± 2375	<.001
$Myoglobin_{max}$, ng/mL	8388 ± 10,811	838 ± 2320	<.001
CKD			
Creatinine, mg/dL	1.6 ± 1.1	1.2 ± 1.0	.030
eGFR, mL/min	55 ± 33	77 ± 43	.013
CKD stage, eGFR			
1, ≥90 mL/min	5 (21.7)	76 (32.9)	. . .
2, 60-89 mL/min	4 (17.4)	67 (29.0)	. . .
3, <60 mL/min	9 (39.1)	68 (29.4)	. . .
4, 15-29 mL/min	3 (13.0)	14 (6.1)	. . .
5, <15 mL/min	2 (8.7)	6 (2.6)	. . .
3-5, <60 mL/min	14 (60.9)	88 (38.1)	.044
Blood cell count			
White blood cells, nL^{-1}	13.2 ± 5.4	8.9 ± 3.1	<.001
Hemoglobin, g/dL	13.1 ± 5.4	13.6 ± 1.9	.100
Hematocrit, %	38.6 ± 7.2	40.3 ± 5.0	.139
Platelets, nL^{-1}	234 ± 106	238 ± 92	.683
Inflammation markers			
CRP, mg/L	9.8 ± 8.7	2.1 ± 3.8	<.001
Fibrinogen, g/L	6.1 ± 2.1	4.7 ± 1.6	.004

CK, Creatine kinase; *CKD,* chronic kidney disease; *CRP,* C-reactive protein; *eGFR,* estimated glomerular filtration rate; *LDH,* lactate dehydrogenase.
[a]Categoric data are presented as number (%); continuous data as mean ± standard deviation.

values of ≥0.01 ng/mL and 3.2 (95% CI, 1.3-7.9) for cTnT values of ≥0.03 ng/mL.

Elevated cTnT and comorbidities. When compared with patients with cTnT values <0.01 ng/mL, patients with higher cTnT levels more frequently presented with diabetes, CAD, atrial fibrillation, a history of cerebral infarction, and impaired renal function (Table III). An elevated cTnT was also associated with higher levels of skeletal muscle enzymes (ie, CK, myoglobin, lactate dehydrogenase). Apart from local thrombolysis, which was less frequently performed in patients with elevated cTnT values (39.4% vs 58.5%, $P = .008$), there was no difference in revascularization procedures performed between the groups (Table IV) or the interval between symptom onset and revascularization (2.9 vs 2.5 days, $P = .158$). We observed a higher rate of in-hospital mortality among patients with cTnT values ≥0.01 ng/mL compared with patients with normal cTnT values (11.3% vs 1.1%; $P < .001$). No significant difference for cTnT levels was observed in the amputation rate, but the case number was too small to draw definitive conclusions.

Elevated cTnT and renal function. Impaired renal function was more frequently observed in patients with worse in-hospital outcomes, as represented by higher levels of serum creatinine (1.6 ± 1.1 vs 1.2 ± 1.0 mg/dL; $P = .03$) and a lower eGFR (55 ± 33 vs 77 ± 43 mL/min; $P = .01$; Table II). Furthermore, we observed higher rates of elevated cTnT and higher rates of mortality or amputation with decreasing eGFR or rather higher stages of CKD (Fig, *A* and *B*). However, nine of 23 patients (39%) who died or underwent amputation (Table I) and 25 of 71 patients (35%) with cTnT values ≥0.01 ng/mL (Table III) had eGFR values within the reference range.

Multivariate Cox regression analysis. After adjustment for age, sex, eGFR, CRP, the presence or absence of known CAD, current smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, and the interval between symptom onset and revascularization, the risk of death or amputation remained increased with cTnT ≥0.01 ng/mL (HR, 3.4; 95% CI, 1.3-8.5; $P = .01$) and was even higher with cTnT ≥0.03 ng/mL (HR, 4.5; 95% CI, 1.7-11.9; $P = .02$). Fitting of additional models showed that the adjusted HR of death or amputation associated with an impaired kidney function was higher among patients with CKD stages 3 to 5 (HR, 3.0; 95% CI, 1.1-8.1; $P = .033$) compared with patients with normal kidney function. The presence of CAD, a higher CRP, and a longer period between symptom onset and revascularization were identified as additional risk factors, whereas age, sex, diabetes mellitus, hypertension,

Table III. Patient characteristics according to cardiac troponin T levels at baseline

Variable[a]	*Cardiac troponin T*		P
	≥0.01 ng/mL (n = 71)	*<0.01 ng/mL (n = 183)*	
Age, years	78 ± 12	69 ± 13	<0.001
Male sex	44 (62)	111 (61)	.887
Vascular risk factors and comorbidities			
Current smoker	9 (13)	55 (30)	.004
Diabetes mellitus	35 (49)	40 (22)	<.001
Arterial hypertension	60 (85)	153 (84)	.861
Hypercholesterolemia	42 (59)	133 (73)	.049
Coronary artery disease	32 (45)	59 (32)	.060
Atrial fibrillation	39 (56)	39 (21)	<.001
Prior cerebral infarction	12 (17)	13 (7)	.032
Prior peripheral vascularization			
Endovascular revascularization	30 (42)	88 (48)	.484
Bypass surgery	9 (13)	48 (26)	.020
Prior amputation	11 (16)	9 (5)	.008
PAOD characteristics			
Rutherford category			
I	18 (25)	72 (39)	.041
IIA	13 (18)	64 (35)	.010
IIB	40 (56)	47 (26)	<.001
Ankle-brachial index	0.18 ± 0.40	0.19 ± 0.28	.117
Time since symptom onset, days	2.5 ± 2.6	2.9 ± 2.6	.041
Renal function parameters			
Creatinine, mg/dL	1.9 ± 1.6	0.9 ± 0.3	<0.001
eGFR, mL/min	45 ± 30	85 ± 42	<.001
CKD 3-5 (eGFR <60 mL/min)	46 (65)	56 (31)	<.001
End-stage renal disease	9 (13)	0 (0)	<.001
Skeletal muscle enzymes			
CK (U/mL)	623 ± 1150	239 ± 521	.010
CK-MB (U/mL)	36 ± 60	21 ± 14	.004
LDH (U/mL)	265 ± 114	196 ± 59	<.001
CK_{max} (U/mL)	1672 ± 3384	811 ± 2545	.003
$Myoglobin_{max}$ (ng/mL)	3163 ± 4964	1057 ± 4563	<.001

CK, Creatine kinase; *CKD,* chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *LDH,* lactate dehydrogenase; *PAOD,* peripheral arterial occlusive disease.

[a]Categoric variables shown as number (%); continuous variables as mean ± standard deviation.

hypercholesterolemia, or current smoking were not independently predictive (Table V).

Elevated cTnT and evidence of myocardial ischemia. No patient included in this analysis presented with clinical symptoms indicating an ACS. Patients with an ACS ≤14 days before ALI had been excluded from the analysis. In addition, the interpretation of ECGs performed upon admission to the hospital did not reveal a difference in the frequency of ECG criteria indicative for acute myocardial infarction in patients with and without elevated cTnT, although there was a trend for a higher frequency of ST depression or T inversion, or both, among patients with elevated cTnT (Table VI).

DISCUSSION

In the present study, we examined the association between elevated cTnT on admission to the hospital and in-hospital outcomes in patients with acute lower limb ischemia. More important, we assessed the risk of in-hospital death or amputation in patients without clinical evidence of acute myocardial ischemia according to the latest version of the ESC/ACCF redefinition of myocardial infarction consensus document.[1] The cutoff concentrations used for cTnT were ≥0.01 ng/mL (99th percentile in a reference population) and ≥0.03 ng/mL (cutoff for the definition of myocardial necrosis).[16] All patients underwent an endovascular approach to re-establish arterial blood flow.

Elevated vs normal cTnT, as defined by any of the cutoff concentrations, was associated with an increased risk of death or amputation in our cohort. Even small elevations of cTnT to levels that were lower than those used to diagnose acute myocardial infarctions were associated with a worse in-hospital outcome in patients with ALI, even after adjusting for potential confounders, such as age, sex, eGFR, CRP, the presence or absence of CAD and traditional vascular risk factors, and the interval between symptom onset and revascularization. The cut-off level of ≥0.01 ng/mL revealed a 3.4-fold (95% CI, 1.3-8.5) elevated relative risk of in-hospital death or amputation in patients with ALI. However, this result can be mainly attributed to the higher mortality rate of 11.3% among patients with elevated cTnT, whereas the difference in the amputation rates alone was not significant.

Table IV. Endovascular revascularization procedures and outcome according to cardiac troponin T levels

Variables	*Cardiac troponin T, No. (%)*		P
	≥0.01 ng/mL (n = 71)	*<0.01 ng/mL (n = 183)*	
Endovascular revascularization			
Mechanical thrombectomy	41 (57.7)	114 (62.3)	.567
Local thrombolysis	28 (39.4)	107 (58.5)	.008
Catheter thrombus aspiration	22 (31.0)	59 (32.2)	.882
Angioplasty/stenting	52 (73.0)	141 (77.0)	.517
Mechanical atherectomy	1 (1.4)	4 (2.2)	>.99
In-hospital outcome			
Death or amputation	12 (16.9)	11 (6.0)	.013
Death	8 (11.3)	2 (1.1)	<.001
Amputation	4 (5.6)	9 (4.9)	.760

Plasma cTnT levels in healthy subjects are supposed to be ≤0.0001 to 0.0002 ng/mL and are thought to result from a continuous microscopic loss of cardiomyocytes during normal life.[18] There is growing evidence to suggest that an elevation in cardiac troponins indicates an increased risk of cardiac disease and unfavorable outcomes even in a healthy population.

According to the results of the population-based Dallas Heart Study, the prevalence of elevated cTnT (ie, ≥0.01 ng/mL) measured with a standard assay was as low as 0.7% in a representative population sample aged 30 to 65 years.[19] According to recently published study that used a novel, highly sensitive assay, the prevalence of detectable cTnT (ie, ≥0.003 ng/mL) in the same cohort was even higher and was reported to be up to 25.0%.[20] Elevated cTnT values were associated with the presence of structural heart disease and a subsequent risk of all-cause mortality.[19,20] Increased risks of CAD, heart failure, and death associated with detectable cTnT levels in highly sensitive assays were also described in a post hoc analysis of the ARIC (Atherosclerosis Risk in Communities) study and in the Cardiovascular Health Study (CHS) populations.[21,22]

In a Swedish study of elderly men who had no cardiac symptoms at the time of blood sampling, those with an elevated cTnI had an increased risk of death or a first CAD event.[23] Ammann et al[24] studied the prognostic value of cTnI elevations in critically ill patients without evidence of ACS and found that elevated cTnI levels were an independent predictor of 30-day death and decreased left ventricular systolic function. In another study, Pham et al[25] investigated cTnI levels among 366 patients with suspected myocardial infarction but without definite ACS, including 57 patients with low levels of cTnI (0.01-0.03 ng/mL) and 309 patients with cTnI levels <0.01 ng/mL. Low-level cTnI elevations were associated with an increased risk of future cardiovascular events during the 1-year follow-up.[25]

Elevated concentrations of cTns are often observed in patients with advanced CKD but without clinical signs of myocardial ischemia. In a large study that included 733 asymptomatic patients with end-stage renal disease, a high percentage of the patients had elevated concentrations of troponins.[15] The authors reported elevated cTnT prevalences of 82% with a 0.01 ng/mL cutoff and 53% with a 0.03 ng/mL cutoff. In our study, elevated cTnT was prevalent in 28.0% and 14.6% of patients, respectively, when the 0.01 and 0.03 ng/mL cutoffs were applied. We also observed higher frequencies of elevated cTnT with declining renal function. Therefore, it is plausible that the association between cTnT levels and adverse in-hospital outcomes was at least partly due to impaired renal function, which by itself is indicative of an adverse outcome. However, our data reveal that cTnT levels ≥0.01 ng/mL remained an independent predictor of death and amputation, even after adjusting for eGFR, age, sex, the presence or absence of CAD and traditional vascular risk factors, and the interval between symptom onset and revascularization.

Regarding the baseline characteristics, no disturbance of renal function was present in 9 of 23 patients (39%) who died or underwent amputation and 25 of 71 patients (35%) who presented with an elevated cTnT. CAD was unknown in 32 of 71 (45%; Table I), and the ECG was normal in 43 of 71 patients (61%), despite cTnT values ≥0.01 ng/mL on admission to the hospital. Remarkably, no patient suffered a fatal myocardial infarction, but 21 of the 23 patients (91%) with adverse in-hospital outcomes were classified as having level IIB ALI according to the Rutherford classification and a lower ankle-brachial index on admission, which indicates a more severe limb ischemia.

Only recently were cTns identified as a possible risk stratification tool in patients with chronic critical limb ischemia (CCLI). Sarveswaran et al[11] followed up 152 patients with CCLI and without evidence of unstable CAD and found that elevated cTnI levels independently predicted mortality during a 2-year period (HR, 4.2; 95% CI, 1.3-12.7). In another investigation, Rittoo et al[10] found a high prevalence of elevated cTnT among 39 patients (44%) with ALI.[10] Cumulative survival rates after 7 days were 53% for cTnT-positive patients and 100% for cTnT-negative patients. In contrast to our study results, no association was found between the presence of CAD or higher CRP values and death. However, the number of patients included in this study was small.

Landesberg et al[26] and Kertai et al[27] previously demonstrated that even low levels of asymptomatic troponin elevation during the perioperative period are associated with a poorer long-term outcome in patients undergoing major vascular surgery.[26,27] The causes of cTnT elevation in patients without clinical symptoms of acute myocardial ischemia are not completely understood. First, given the association between CAD and PAOD, it is very likely that patients with elevated troponins had more severe coronary heart disease. Subclinical myocardial damage may result from transient or less severe ischemia and as a consequence of the exposure of myocardial cells to cytokines. In these

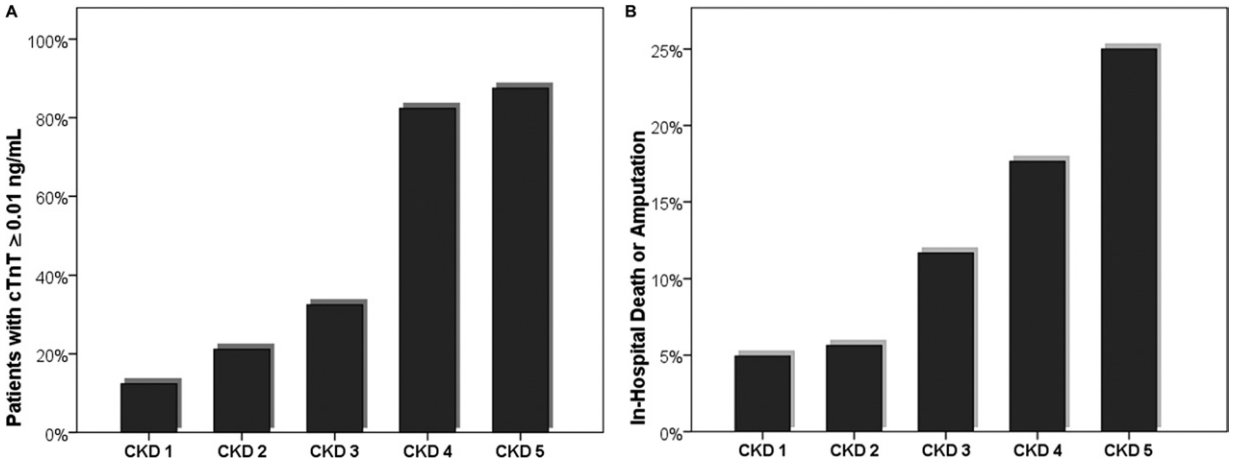

Fig. A, Prevalence of elevated cardiac troponin T (*cTnT* ≥0.01 ng/mL) and **(B)** in-hospital death or amputation in acute limb ischemia patients according to the chronic kidney disease classification by estimated glomerular filtration rate: I, >90 mL/min; II, 60 to 89 mL/min; III, 30 to 59 mL/min; IV, 15 to 29 mL/min; V, <15 mL/min or dialysis.

Table V. Univariate and adjusted hazard ratios (*HR*) for worse in-hospital outcomes

	Univariate		*Adjusted*	
Variable	*HR (95% CI)*	P	*HR (95% CI)*[a]	P
Cardiac troponin T				
≥0.01 ng/mL	3.1 (1.3-7.2)	.009	3.4 (1.3-8.5)	.010
≥0.03 ng/mL	3.6 (1.5-8.7)	.004	4.5 (1.7-11.9)	.020
CKD stages III–V	2.4 (0.9-5.7)	.058	3.0 (1.1-8.1)	.033
CAD	2.8 (1.1-7.2)	.040	4.3 (1.3-14.6)	.019
CRP >0.5 mg/L	6.6 (1.5-28.2)	.011	5.3 (1.2-23.2)	.026

CAD, Coronary artery disease; *CI,* confidence interval; *CKD,* chronic kidney disease; *CRP,* C-reactive protein.

[a]Adjusted for age, sex, estimate glomerular filtration rate, CRP, the presence or absence of known CAD, current smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, and the interval between symptom onset and revascularization.

situations, troponin molecules may leak through reversibly permeabilized plasma membranes into the circulation.[28] Elevation of cardiac troponins has been described for patients with microvascular CAD, which frequently occurs in conjunction with chronic heart failure, diabetes mellitus, and CKD.[23]

In the special situation of ALI, the increase in cardiac troponins seems to be directly associated with rhabdomyolysis. The release of necrotic muscle constituents into the circulation may have direct toxic effects on myocardial cells. With the onset of skeletal muscle ischemia, there is a conversion of muscle metabolism from aerobic to anaerobic that results in an increased production of lactate and the development of acidosis. Potassium, phosphate, CK, and myoglobin are released into the systemic circulation. Cytokine liberation, leukocyte activation, prothrombotic eicosanoid production, activation of the compartment cascade, and formation of toxic oxygen metabolites are consequences of these changes that lead to the clinical manifestation of SIRS.[10,29,30] SIRS may contribute to cardiac and renal dysfunction and lead to multiorgan failure. Remarkably, the cause of death for 8 of 10 patients in our cohort was progressive ischemia, septicemia, and multiorgan failure. The aforementioned mechanisms are further amplified by reperfusion.

ALI is one of the most frequent reasons for amputation. Two primary factors explain the high morbidity and mortality that result from ALI: the underlying comorbidities and the delay in the recognition and treatment of ischemia. Even with the extensive use of newer endovascular techniques, amputation rates of 10% to 25% are reported, and mortality is approximately 10%.[14,31] Older age, a lower body weight, significant underlying atherosclerosis, and the presence of diabetes mellitus, chronic heart failure, CKD, and malignancy have been previously identified as predictors of poorer in-hospital outcomes.[31] The results of the Surgery vs. Thrombolysis for Ischemia of the Lower Extremity (STILE) and Thrombolysis or Peripheral Arterial Surgery (TOPAS) studies suggest the equivalence of endovascular or surgical therapies, as measured by death or amputation.[32,33]

At our institution, a primary endovascular approach combining different techniques, such as mechanical thrombectomy, catheter thrombus aspiration, local thrombolysis, percutaneous transluminal angioplasty and stent placement, and atherectomy, was chosen to re-establish blood flow to the ischemic lower limb. The rates of in-hospital mortality and amputation in our cohort were unexpectedly low (3.8% and 5.1%, respectively). These favorable results may be explained by the combination of different techniques for revascularization depending on the anatomic location and the short duration between the onset of symptoms and the revascularization procedure.

Our study has some important limitations. First, this is a retrospective study design. Because patients presented with ALI that required a rapid revascularization strategy in

Table VI. Prevalence of electrocardiograph criteria indicative for acute myocardial ischemia in patients with and without elevated cardiac troponin T[a]

Variable	*Cardiac troponin T, %*			*Cardiac troponin T, %*		
	≥0.01 ng/mL (n = 71)	*<0.01 ng/mL (n = 183)*	P	*≥0.03 ng/mL (n = 37)*	*<0.03 ng/mL (n = 217)*	P
ST elevation	3.4	2.7	>.99	0.0	3.1	>.99
ST depression and/or T inversion	31.4	23.0	.060	37.9	25.0	.201
Left bundle branch block	4.2	1.0	.339	0.0	1.7	>.99

[a]According to the consensus document of the Joint European Society of Cardiology (ESC)/American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Redefinition of myocardial infarction.[1]

most cases but had no clinical symptoms of myocardial ischemia, we lack serial troponin measurements. Therefore, we cannot distinguish accurately between elevations due to acute silent myocardial ischemia and chronic disease, which is a major limitation to the interpretation of our results. According to the consensus statement of the ESC/ACCF/AHA/WHF Task Force, a rise and/or fall in cardiac biomarkers, in addition to clinical symptoms of ischemia or typical ECG changes, is required for the diagnosis of myocardial infarction.[1] However, patients with unfavorable outcomes presented more frequently with ST segment depression or T inversion that were possibly indicative of silent myocardial ischemia, even though this difference was not significant. Because we only examined the ECG performed at hospital admission, we are not certain whether the ECG changes were really "new," as required for the diagnosis of acute myocardial ischemia.

Second, there is evidence that patients with elevated troponins in our cohort had higher rates of diabetes mellitus, chronic renal failure, CAD, and prior cerebral infarction. Therefore, it can be supposed that those patients who had more serious comorbidities underwent more cautious or less ideal revascularization procedures. Indeed, we observed that local thrombolysis was performed less frequently among patients with elevated cTnT, which might be attributed to the potentially higher bleeding risk. However, there was no difference between the other revascularization procedures performed in patients with and without elevated cTnT.

Finally, overall rates for mortality and amputations in our study were low, thereby explaining the low number of patients with poorer in-hospital outcomes.

CONCLUSIONS

Among patients with ALI and without clinical symptoms suggesting myocardial ischemia, elevated cTnT levels at the time of hospital admission can identify patients at risk of in-hospital death or amputation. Even small elevations of cTnT (≥0.01 ng/mL) predict a markedly increased risk of poorer in-hospital outcomes. In addition to serial cTnT measurements and ECG recordings to rule out silent myocardial ischemia, these patients deserve intensive care and monitoring of cardiac function after immediate endovascular revascularization for ALI.

AUTHOR CONTRIBUTIONS

Conception and design: BL, TZ
Analysis and interpretation: BL, TS
Data collection: BL, TS, SS, AR, US, EN, KB, UB, TZ
Writing the article: BL
Critical revision of the article: SS, AR, US, EN, KB, UB, TZ
Final approval of the article: BL, TS
Statistical analysis: BL, TS
Obtained funding: Not applicable
Overall responsibility: BL

REFERENCES

1. Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC, ACCF/AHA/WHF Task Force for Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-38.
2. Hafner G, Thome-Kromer B, Schaube J, Kupferwasser I, Ehrenthal W, Cummins P, et al. Cardiac troponins in serum in chronic renal failure. Clin Chem 1994;40:1790-1.
3. Wayand D, Baum H, Schätzle G, Schärf J, Neumeier D. Cardiac troponin T and I in end-stage renal failure. Clin Chem 2000;46:1345-50.
4. Abbas NA, John RI, Webb MC, Kempson ME, Potter AN, Price CP, et al. Cardiac troponins and renal function in nondialysis patients with chronic kidney disease. Clin Chem 2005;51:2059-66.
5. Baum H, Obst M, Huber U, Neumeier D. Cardiac troponin T in patients with high creatinine concentration but normal creatine kinase activity in serum. Clin Chem 1996;42:474-5.
6. Ellis K, Dreisbach AW, Lertora JL. Plasma elimination of cardiac troponin I in end-stage renal disease. South Med J 2001;94:993-6.
7. Fredericks S, Chang R, Gregson H, Bewick M, Collinson PO, Gaze D, et al. Circulating cardiac troponin-T in patients before and after renal transplantation. Clin Chim Acta 2001;310:199-203.
8. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. Circulation 2005;112:3088-96.
9. Koutouzis M, Sfyroeras G, Moulakakis KG, Kontaras K, Nikolaou N, Besias N, et al. Cardiac troponin I in patients with acute upper and lower limb ischemia. VASA 2008;37:327-32.
10. Rittoo D, Stahnke M, Lindesay C, Grocott E, Hickey N, Downing R. Prognostic significance of raised cardiac troponin T in patients presenting with acute limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:500-3.
11. Sarveswaran J, Ikponmwosa A, Asthana S, Spark JI. Should cardiac troponins be used as a risk stratification tool for patients with chronic critical limb ischaemia? Eur J Vasc Endovasc Surg 2007;33:703-7.
12. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339:799-805.Herzog CA, Ma JZ, Collins AJ.

13. Pasqualini L, Schillaci G, Pirro M, Vaudo G, Siepi D, Innocente S, et al. Renal dysfunction predicts long-term mortality in patients with lower extremity arterial disease. J Intern Med 2007;262:668-77.
14. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1-S75.
15. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002;106:2941-5.
16. Hermsen D, Apple F, Garcia-Beltràn L, Jaffe A, Karon B, Lewandrowski E, et al. Results from a multicenter evaluation of the 4th generation Elecsys troponin T assay. Clin Lab 2007;53:1-9.
17. National Kidney FoundationK/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39;(2 Suppl 1):S1-S266.
18. Tate JR. Troponin revisited 2008: assay performance. Clin Chem Lab Med 2008;46:1489-500.
19. Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958-65.
20. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503-12.
21. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123: 1367-76.
22. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494-502.
23. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 2006;113:1071-8.
24. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol 2003; 41:2004-9.
25. Pham MX, Whooley MA, Evans GT Jr, Liu C, Emadi H, Tong W, et al. Prognostic value of low-level cardiac troponin-I elevations in patients without definite acute coronary syndromes. Am Heart J 2004;148:776-82.
26. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547-54.
27. Kertai MD, Boersma E, Klein J, Van Urk H, Bax JJ, Poldermans D. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28:59-66.
28. Wu AH. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? Intensive Care Med 2001;27:959-61.
29. Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. Semin Vasc Surg 2009;22: 29-33.
30. Punukollu G, Gowda RM, Khan IA, Mehta NJ, Navarro V, Vasavada BC, et al. Elevated serum cardiac troponin I in rhabdomyolysis. Int J Cardiol 2004;96:35-40.
31. Zeller T, Tepe G. Treatment of acute limb ischemia with focus on endovascular techniques. VASA 2009;38:123-33.
32. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. Ann Surg 1994;220:251-66.
33. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. N Engl J Med 1998;338:1105-11.

Submitted Jul 7, 2011; accepted Oct 6, 2011.